IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Review Article**
April 2021 Vol.:21, Issue:1


# Stroke - A Review on Current Trends

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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**Submitted:** 20 March 2021
**Accepted:** 27 March 2021
**Published:** 30 April 2021


www.ijppr.humanjournals.com

**Keywords:** Stroke, Neurologic disorder, Antiplatelets, Anticoagulants

**ABSTRACT**

Stroke is a very common Neurologic disorder worldwide and is known to be the fourth killer in the United States. Due to expensive Hospitalization charges & ever increasing number of patients, it exerts a burden for Healthcare providers. The burden increases by folds in the developing Countries. Pharmacological treatment and Surgery are the recommended treatment modalities. Drug treatment with Antiplatelets & Anticoagulants is the treatment of choice. Secondary prevention by use of Antihypertensives, Statins &smoking cessation is recommended. Advanced treatments for Stroke has reached a modern State of development in this era of digital & device technology. Neurointerventional techniques have enabled surgical procedures in brain by bypassing the need of opening the skull, & this has provided an excellent alternative for treatment of different Cerebrovascular diseases & Stroke. In advanced cases of Stroke, surgery can be beneficial. The newer interventional procedures include Microcatheter-based surgical interventions, use of Clot Retrieval Devices, Pneumbra – Microcatheter based system device, and Stentriever- The newest embolectomy devices for Stroke patients. Carotid Endarterectomy Surgery [CEA] & Carotid Angioplasty and Stenting are the Preventive Surgical procedures for stroke.

## INTRODUCTION-

Stroke is one of the most common Neurological disorders Worldwide. In 2016, it was found out that Neurological disorders were the leading cause of DALYs(disability-adjusted life-years; the sum of years of life lost [YLLs] and years lived with disability [YLDs] ). Stroke being the leading contributor of Neurological DALYs out of the Top 4 Neurological disorders. [1] It is known to be the Fourth killer in the United States, It is estimated that approximately 800,000 primary (first-time) or secondary (recurrent) strokes occur annually in the U.S., with major predisposition towards Primary Strokes(roughly 600,000).[2]Whereas In India, the burden of Communicable and Non-Communicable diseases is double. Studies have shown that the incidence rate of Stroke in India is 119-145/100,000; Kolkata being the highest with the Fatality rates.[3]

## DEFINITION-

In 1689, William Cole for the very first time introduced the term 'Stroke' in Medicine. Before this, "Apoplexy', was the term coined by Hippocrates (400 B.C), that was commonly used to refer to acute Non-traumatic injuries of the brain. Amidst 1950s, Physicians felt there was a need to introduce a term for temporary vascular episodes of brain that will not qualify as Stroke, and thus, TIA (Transient Ischemic Attack) came into picture. Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause. [4]Stroke is "a State of focal Neurological deficit of an abrupt onset, presumably of vascular origin, which can last for at least 24 hours".[5]In 1970s, WHO came up with the definition of Stroke(used till now), it defines Stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin."[6]

## EPIDEMIOLOGY-

Currently, there are 7.2 million stroke survivors in the United States and worst outcomes seen in women. Due to expensive posthospitalization rehabilitation and nursing home care, the annual cost of stroke is estimated to be $40.1 billion in the United States.[7]In the United States, the direct & indirect costs of Stroke care is estimated to be $68.9 billion for the year 2009.[8]The Stroke rates in African-Americans are 1.5 times than the Whites. Stroke incidences are also influenced by Geographic differences, like the States in the Southeastern

United States have shown Stroke mortality rates 30% to 40% higher than the national average. [9]. Case fatality is more with Haemorrhagic Strokes (50%), while it is 20% for Ischaemic Strokes.[10]

**ETIOLOGY-**

Broadly, Stroke is categorized as either Ischaemic (85%) or Haemorrhagic (15%). [11] The latter type is further divided into subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). Following a trauma or due to rupture of an intracerebral aneurysm or arteriovenousmal formation (AVM) can cause blood to enter into the subarachnoid space which leads to SAH. Whereas if bleeding is in the brain parenchyma itself, along with the formation of a hematoma in the brain, this condition is referred as ICH. ICH is most commonly precipitated by Uncontrolled Hypertension, also antithrombotic therapy, cerebral amyloid angiopathy and drugs of abuse are also known to cause ICH.[12] Ischaemic Stroke is due to either

- Formation of a local thrombus (thrombotic Stroke 60%) or
- Due to embolism (embolic Stroke 20%) both result in occlusion of cerebral artery.

Embolic infarcts survive better than Thrombotic infarcts. Occlusion of fine perforating vessels or fine arterioles, may result in multiple smaller infarcts of less than 5mm in diameter, referred to as Lacunar infarcts. TIA (Transient Ischaemic Attack) is sometimes referred to as "mini-stroke". "It is different from the major types of stroke because blood flow to the brain is blocked for only a short time—usually no more than 5 minutes.[13] It is a a temporary deficit of neurological or monocular functions of acute onset, which lasts for less than 24 hours". Approximately 30% of the Stroke patients have a history of TIA. An interruption in the supply of blood to the brain due to cerebral dysfunction or temporary Cerebral Ischaemia leads to TIA. Cerebral Ischaemia due to embolisation is another important cause of TIA. Carotid Ischaemia (atherosclerotic changes in carotid artery) or Vertebrobasilar Ischaemia (occurring in subclavian artery proximal to vertebral artery) may also cause TIA. [14] Cryptogenic Stroke "a Stroke of unknown cause", despite testing the cause for this type of Stroke cannot be determined. Brain Stem Stroke occurs in the brain stem; it can affect the body bilaterally and the subject may remain in a 'locked-in' state. In such a condition the patient is generally unable to speak or move below the neck. [15]

**RISK FACTORS-**

For Ischaemic Stroke, Risk factors can be non-modifiable or modifiable.

➢ Non-Modifiable Risk factors:

- Age-The risk of stroke doubles for each decade older than 55 years.
- Gender-Men are ata higher risk than women at a younger age, but women have a higher mortality and higher lifetime risk of ischemic stroke overall.
- Ethnicity- African Americans, Asian-Pacific Islanders, and Hispanic individuals have higher mortality rates from ischemic stroke than Caucasians.[16]
- Family History- Genetic Disorders like Sickle Cell disease may lead to Stroke. The risk increases more when heredity combines with unhealthy lifestyle, unhealthy diet, smoking etc.[17]

➢ Modifiable Risk Factors:

- Previous Stroke or Transient Ischemic Attack- A previous history of TIA increases the risk of Stroke.
- High Blood Pressure- Advised to check Bp often. Lifestyle modifications or antihypertensive medication to be initiated.
- High Cholesterol- A waxy, fatty substance synthesized by the liver (endogenous Cholesterol) or it is also present in various foods. (Exogenous Cholesterol) If present in excess, it may get deposited in arteries, even of brain and result in stroke and other conditions. Lipid profile testing is recommended.
- Heart Diseases- Many heart disorders increase the risk of Stroke. E.g. In CAD, the plaque in the artery is responsible for interruption of the blood flowing to the arteries resulting in Stroke. Other conditions, like irregular heartbeat, defect in the heart valves can even lead to Stroke.
- Diabetes- High Blood Sugar levels interrupt the flow of oxygen and other nutrients to different parts of the body including brain, and thus results in stroke. Elevated Bp in diabetic patients can again be a trigger for Stroke.

- Sickle Cell Disease- It is a blood disorder associated with Ischaemic-Stroke common in Black and Hispanic Children. The flow of blood to the brain may get obstructed due to the presence of Sickle cell in the vessel. [18]

- Studies have shown that there is an overall 29 percent increased risk of Stroke especially, ischaemic Stroke in patients receiving Hormone Replacement therapy[HRT].[19]

➢ Behavioral triggers include-

- Unhealthy Diet- Excessive Salt intake can increase the risk of Hypertension and thus Stroke. Diet rich in Cholesterol, Trans & saturated fats can increase the risk of Stroke and heart diseases.

- Physical Inactivity

- Alcohol- It can elevate Bp, and increase the risk of Stroke. Alcohol may also increase the level of TGs in blood which can stiffen the arteries.

- Obesity- Excess of body fat (low good cholesterol & High bad Cholesterol) may trigger Diabetes, Hypertension and thus Stroke.

- Tobacco Smoking- The nicotine in cigarettes may elevate Bp, and the CO present in cigarette smoke may reduce the oxygen carrying capacity of blood. [20]

➢ Potentially Modifiable Less Well Documented Risk Factors-

- Migraine

- Metabolic Syndrome

- Inflammation & Infection

- Elevated lipoprotein

- Homocysteinemia

- Sleep disordered breathing

- Drug abuse [21]

**PATHOPHYSIOLOGY-**

Ischaemic Stroke-

Occlusion in the blood flow of cerebral artery results in this condition. Conditions like Stroke, Chronic HTN, and Atherosclerosis impair the cerebral autoregulation (process by which cerebral blood flow is maintained at a rate of 50ml/100g per minute). Decrease in the cerebral blood flow will lead to infarction of cerebral tissue. Surrounding this infracted tissue is an area which is Ischaemic but maintains membrane integrity, it is called as Ischaemic Penumbra. There are three main mechanisms known to cause Ischaemic stroke-

- Occlusion of cranial blood vessels due to an embolus from a distant site
- In situ thrombosis of an intracranial blood vessel
- Hypoperfusion due to stenosis of extracranial artery [22]

In Ischaemic Stroke, due to decreased oxygen supply, there is depletion in the ATP levels and accumulation of lactate and intracellular Sodium and water resulting in cytotoxic edema and cell lysis. Influx of Calcium causes activation of Lipases & Proteases, which causes protein degradation & fatty acid release from membranes. There is also the release of excitatory Amino acids like glutamate & aspartate that causes neuronal damage. [23]

**Haemorrhagic Stroke-**

Following bleed sites are common- cerebral lobes, basal ganglia, the thalamus, cerebellum and brain stem. ICH hematoma leads to primary injury and compression of the parenchyma of brain, disrupting the neurons and glia. As a result, neurotransmitter release, oligaemia and cellular swelling occur. Released Thrombin activates microglia, causes inflammation and edema.

Increase in intracranial pressure (ICP) & compression by hematoma results in Primary injury. Whereas Inflammation, disruption of BBB & formation of reactive species and radicals results in Secondary injury. [24]A low Glasgow Coma Score (GCS 3-4), ICH volume >30 cc (mL), intraventricular extension, and age> 80 are associated with Higher mortality rates.[25]

**CLINICAL PRESENTATIONS-**

- Sudden weakness, numbness often unilaterally

- Difficulty in understanding speech, trouble in speaking
- Sudden trouble seeing
- Trouble in walking, loss of balance
- Sudden severe headache

If someone is having Stroke, the patient is spotted by using F.A.S.T. criteria-

F—Facial drooping

A - Arm weakness

S - Speech: There may be difficulty in speaking

T - Time: If these signs are seen, call 9-1-1 right away. [26]

**DIAGNOSIS-**

Laboratory Parameters: Treatment eligibility is assessed after estimation of lab parameters like blood glucose, platelet count, and other coagulation parameters such as PT, aPTT. If the exact cause of Stroke is not known, testing for Hypercoagulable states is done. (Protein C/S deficiency, APL antibodies). [27] Serum biomarkers used are S100 calcium binding protein B or S100B, glial fibrillary acidic protein, bnp, and matrix metalloproteinase-9. These biomarkers are not routinely measured by the laboratories but are of importance in Clinical Research. [28] Other Diagnostic Tests-

- CT scan – A CT Scan of head will show regions of hyperintensity (White) in patients with Hemorrhage in comparison, regions with hypointensity will appear dark in patients with Infarction.

CT Scan is done with contrast for infarcts, & for haemorrhagic Stroke, it is performed without contrast.

- MRI- Tells about the regions of Ischaemia with higher resolution; MRI with diffusion-weighted imaging (DWI) tells about emerging infarct within minutes of stroke onset.

CT Scans are more preferred than MRI in strokes.

- Vascular imaging with CTA (Computed Tomography Angiography) - In patients with endovascular treatment recommendation, it helps in identification of acute treatment candidacy, and arterial stenosis (intra & extra cranial).

- ECG- To check for the presence of Atrial fibrillation, or arrhythmias which are potent triggers for Stroke.

- TTE (transthoracic echocardiogram) - For detection of Cardiac-valve abnormalities and sources of emboli to the brain. A "bubble-study" is done to reveal atrial-septal defect or potent foramen ovale.

- In patients who cannot undergo CTA, CD (Carotid Doppler) is performed. It tells about the extent of stenosis in the carotid arteries supplying to the brain. A TCD (transcranial Doppler) also tells about stenosis (extra cranial or intracranial).[29]

For Haemorrhagic Stroke, differential diagnosis includes acute hypertensive crisis, acute subdural hematoma, pituitary apoplexy, meningitis, cervical artery dissection, cerebral venous thrombosis, reversible cerebral vasoconstrictive syndrome (RCVS), dural sinus thrombosis, hemorrhagic infarct and hemorrhagic neoplasm. The Radiographic imaging techniques mentioned above may help in ruling them out.[30]



**TREATMENT-**

Goals of treatment include prevention of mortality and long-term disability, preventing complications other than immobility & neurologic dysfunction and to Prevent Stroke recurrence. [31]

- Blood Pressure Management- It is recommended to do a gradual reduction of blood pressure to 150/90mmHg. Beta-blockers (labetalol, esmolol), channel blocker (nicardipine), ACE inhibitor (enalapril), or hydralazine is recommended. Bp should be monitored every 10-15 minutes. [32] High SBP is related with neurological deterioration and death.[33] ASA [American Stroke Association] recommends that In ICH and elevated bp, acute lowering of SBP to 140 mm Hg has been shown to be safe and may improve functional outcome.[34] ATACH [Antihypertensive Treatment in Acute Cerebral Hemorrhage] Study &INTERACT [Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial] study are the trails which are going on the optimal management of hemorrhagic stroke. [35]As per the ATACH Study, there exists a nonsignificant relationship between the magnitude of systolic blood

pressure (SBP) reduction and hematoma expansion and 3-month outcome.[36]Whereas, As per INTERACT Study, it has been observed that intensive BP-lowering attenuated hematoma growth over 72 hours.[37]Pharmacological options available for Bp lowering in Acute Stroke include-

- Labetalol 10-20mg IV over 1-2 mins, may repeat.
- Nicardipine 5mg/hr IV, titrate 2.5mg every hour every 5-15mins, maximum 15mg/hr
- Clevidipine1-2mg/hr IV, titrate by doubling the dose every 2-5 mins, maximum 21mg/hr
- Others- Enalapril, Hydralazine, Nitroprusside IV infusion, Labetalol IV infusion. [38]

Following Bp management guidelines are to be followed after Ischaemic Stroke in order to prevent future Strokes-

-If adults with previously treated hypertension experience a stroke or TIA, they should be restarted on antihypertensive treatment after first few days to reduce the risk of recurrence of Stroke & other vascular events.

-In adults who experience a stroke or TIA, a thiazide diuretic, ACE inhibitor, or angiotensin receptor blocker, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful. [39]

- Elevated Intracranial Pressure (ICP) Management-Elevate the head of the bed to 30 degrees and use of osmotic agents (mannitol, hypertonic saline). Dosing- 20 % mannitol - 1.0 to 1.5 g/kg.[40]If there is a further rise in ICP, hyperventilation after intubation and sedation may be done. As per ASA(American Stroke Association), ICP is monitored with a parenchymal or ventricular catheter with Glasgow coma scale (GCS) <8 or those with evidence of transtentorial herniation or hydrocephalus.[41]

- Hemostatic therapy-Recommended to reduce the progression of hematoma.[42] Prothrombin complex concentrates (PCCs), fresh frozen plasma (FFP), recombinant activated factor VII (rFVIIa), Vitamin K etc. are used. ASA recommends that in Thrombocytopenia patients should receive platelet concentrate. [43] As per the FAST trial, it was observed that rFVIIa reduces the growth of hematoma but doesn't improve survival or functional outcome.[44]

- Temperature Management- Fever can worsen in both types of Strokes. It is recommended to identify the cause and treat it accordingly with Pharmacological & Nonpharmacological interventions.[45]

- Statins- In order to reduce Stroke recurrence, Statin therapy is recommended for all patients of Ischaemic Stroke. The statins have shown to reduce the risk of stroke by 30% in patients with CAD & elevated plasma lipids.[46] For patients with age greater than 75, ischaemic stroke of presumed atherosclerotic origin should be treated with high intensity statin therapy, it is suggested that there is a 50% or greater reduction in LDL. [47] Atorvastatin 10mg/day or a combination Atorvastatin 10mg/day+ezetimibe 10mg/day Orally.

- Cerebroprotection- There is oxidative stress, inflammation, toxicity of thrombin & erythrocyte lysates in Secondary injury of Haemorrhagic Stroke. So, different strategies to overcome this should be used. In order to reduce the inflammatory damage, celecoxib, misoprostol & pioglitazone are used. To reduce oxidative stress nicotinamide mononucleotide, flavonoid & Edaravone are used. Use of iron chelator deferoxamine is in experimental phase. Nimodipine, which is a Calcium Channel blocker improves SAH outcomes by neuroprotection. [48]

- Antiepileptic therapy- About 3-17% of the patients have seizure in first two weeks and 30% patients on EEG monitoring show electrical seizure activity.[49]

Management of Ischaemic Stroke-

The guidelines of Stroke council of ASA suggest the use of only two pharmacologic agents with class I recommendations, these are alteplase which has to be started within 4.5 hours and aspirin to be started within 24 to 48 hours of stroke onset. [50]

- Alteplase- It is a recombinant tPA(tissue plasminogen activator),rt-PA. Use of Alteplase has a high risk of bleeding, ICH. In order to achieve a positive outcome & to minimize the risk, it is essential to adhere to the guideline-recommended protocol. Essentials of the protocol include-

  - Stroke team activation
  - CT scan to rule out hemorrhage
  - Treatment within 4.5 hours of symptom onset

- To meet the inclusion & exclusion criteria.
- administer Alteplase 0.9mg/kg total dose as 10% as bolus over 1 minute, and remaining 90% over 1 hour, to a maximum of 90mg dose.
- Avoid antithrombotic therapy(antiplatelet/anticoagulant) for 24hours after alteplase
- Monitor for elevated Bp, hemorrhage & neurologic status. [51]

- Aspirin- Exerts antiplatelet effect by irreversibly inhibiting cox, which further prevents the conversion of Arachidonic acid to TXA2, latter one is a powerful vasoconstrictor & stimulator of platelet aggregation. Aspirin also inhibits PGI2 activity in smooth muscles. PGI2 inhibits platelet aggregation. Recent studies show that the lowest effective dose may be 50 mg/day. Common dose-related GI adverse effects include Upper gastrointestinal (GI)discomfort and bleeding. As per current Recommendations, it is advised to administer aspirin at least 2 hours before an NSAID or to wait at least 4 hours after an NSAID dose.[52] It should never be given within 24 hours of tPA administration as it would increase the risk for bleeding. However, daily aspirin 325mg orally, may be given after 24 hours but within 48 hours of Stroke onset.

- Blood Pressure management
- Statin therapy
- Secondary prevention of Stroke

Management of TIA-

- Use of antiplatelet drugs, low dose Aspirin (325mg oral), or Clopidogrel 75mg orally daily. Or, combination of Aspirin 25mg+ER dipyridamole 200mg orally twice daily.
- Statin therapy for management of adverse lipid profile
- Blood Pressure Management
- Cessation of Smoking [53]

Secondary Prevention of Stroke-

For Secondary prevention of Stroke, the recommended drugs include Aspirin, extended-release dipyridamole plus aspirin, and clopidogrel. In patients with Cardiac source of embolism, Oral anticoagulants like either apixaban, Vitamin K antagonist (Warfarin), rivaroxaban, Dabigatran is recommended. [54] Other Approaches include use of Statin therapy &Bp Management for Secondary prevention. [55]

- Antiplatelet agents- Patients with a history of acute ischemic stroke or TIA are recommended long-term antithrombotic therapy. Aspirin is the best choice of agent but Current literature favors rhe use of combination of ER dipyridamole+aspirin, clopidogrel as an alternative first line agent.[56]

- Clopidogel- Exerts Antiplatelet effect by inhibiting purigenic receptor P2Y, G-protein coupled 12 (P2Y12), & thus inhibiting the ADP pathway of platelet aggregation. This results in alteration of platelet membrane and interferes with the membrane-fibrinogenic interaction leading to blocking of platelet glycoprotein IIb/IIIa Receptors. It is a prodrug which is converted to its active metabolite by CYP4502C19. A dose of 75mg/day of Clopidogrel is as good as medium-dose of aspirin(325mg/day), & there is less GI bleeding. [57]

- Extended-Release Dipyridamole Plus Aspirin- In high doses, dipyridamole inhibits aggregation of platelets by inhibition of phoshphodiesterase, as a result there is accumulation of cAMP & cGMP, which prevents platelet activation. [58]

- Ticagrelor- It is a direct-acting ADP P2Y12 receptor inhibitor.[59] In SOCRATES trial, Noncardioembolic stroke patients who were not treated with alteplase were given ticagrelor with a loading dose of 180 mg then 90 mg twice daily for 90 days or aspirin 300 mg loading dose with 100 mg daily 90 days. It was demonstrated that there was a 32% lower risk of secondary stroke within 90 days in patients treated with ticagrelor. [60]

- Dual Antiplatelet Therapy- Several studies have shown the efficacy of DAPT (Dual antiplatelet therapy) with clopidogrel, prasugrel or Ticagrelor along with Aspirin, in order to prevent secondary ischemic events like Stroke & TIA. As per the 2018 Guidelines for management of Acute Ischemic Stroke, use of Clopidogrel& Aspirin for prevention of secondary stroke is beneficial if initiated within 24hours of the onset of Stroke & continued for 21-90 days. [61]

- Oral Anticoagulants- Treatment of choice for preventing Stroke occurrence in patients with Atrial fibrillation.[62] As per The European Atrial Fibrillation Trial (EAFT), there was a

53% reduction in risk of Stroke with Oral anticoagulants. [63] The newer DOAC (direct-acting oral anticoagulants) like rivaroxaban, dabigatran (direct thrombin inhibitor), edoxaban, & apixaban (direct factor Xa inhibitor) have more advantages over Warfarin in terms of lesser drug-food interactions & ease of dosing. [64] [65]

Surgery –

- Neurointerventional Procedures-

- Microcatheter-based surgical interventions: Uses a small microcatheter, thrombolytic medication like tPA, can be administered directly towards the occluding thrombus. Comprehensive Stroke Care Centers provide this kind of treatment.

- Clot Retrieval Devices- The Merci Retriever is a device which was approved by FDA in 2004 to remove blood clots from the arteries of Stroke patients.

- Pneumbra – Microcatheter based system device, approved by FDA in 2008.

- Stentriever- The newest embolectomy devices for Stroke patients.

- Preventive Surgical Procedures-

- Carotid Endarterectomy Surgery (Carotid Endarterectomy, CEA)- Using a dissecting tool, the plaque is removed. This restores the normal blood flow. The artery is then repaired with the help of sutures or graft. The entire procedure takes about 2 hours. There can be 1-3% risk of Stroke after the surgery. Restenosis i.e., reblockage of Carotid artery may occur. This is common in cigarette smokers. Temporary nerve damage may lead to numbness of tongue, or face.

- Carotid Angioplasty and Stenting- A newer option that may be effective for patients who are at a very high risk for surgery. In Carotid stenting, a small metal-mesh tube is inserted in the Carotid artery to increase the blood flow. Stent is inserted by a procedure called angioplasty. Embolism is the most common complication that can occur. This can block an artery in the brain & cause Stroke. This risk is minimized by using small filters called embolic protection devices. [66]

Conclusion- The onset of Stroke is indeed discouraging & damaging event for a patient and his/her family. The patient may undergo from complete independence to complete

dependence real quick in this case. It has been a major cause of morbidity & mortality Worldwide. In the very initial stages, a Standardized medical therapy may be successful. Whereas, Surgery can benefit the patient in advanced stages. Advanced treatments for Stroke has reached a modern State of development in this era of digital & device technology. Neurointerventional techniques have enabled surgical procedures in brain by bypassing the need of opening the skull, & this has provided an excellent alternative for treatment of different Cerebrovascular diseases & Stroke.

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